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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,990	WORCEL, MANUEL	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on December 16, 2009.

Status of Claims

Claims 1, 5 and 21-25 are currently pending and are the subject of this office action.

Claims 1, 5 and 21-25 are currently under examination.

Priority

The present application is a 371 of PCT/US05/107384 filed on 03/31/2005, and claims benefit of provisional application No. 60/557,700 filed on 03/31/2004.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103 (Maintained rejection)

Claims 1, 5 and 21-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et. al. (US 6,472,390, cited in prior office action) in view of Adams et. al.(US 6,747,063, cited in prior office action), and over Goodman (US 6,087,398, cited in prior office action) in view of Loscalzo (US 6,635,273, cited in prior office action).

The reasons for this rejection have been provided in the previous office action dated 09/17/09, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues:

Claims 1, 5, and 21-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stamler et al (US 6,472,390) in view of Adams et al (US 6,747,063) and over Goodman (US 6,087,398) in view of Loscalzo (US 6,635,273).

Applicants respectfully traverse the rejection and respectfully submit that the claimed invention is unobvious over the cited reference.

The pending claims 1, 5 and 21 are directed to the treatment of sickle cell anemia comprising administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate and at least one hydralazine compound.

Stamler is cited by the Examiner for the treatment of sickle cell anemia by the administration of a NO donor. Adams is cited by the Examiner in teaching that N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate are NO donors. As pointed out by the Examiner, neither Stamler nor Adams mention of the use of a hydralazine compound (i.e. antioxidant) either alone or in combination with a nitric oxide donor for the treatment of sickle cell anemia. Additionally there is no suggestion or motivation by Stamler or Adams to treat sickle cell anemia by administering a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate in combination with a hydralazine compound.

Goodman is cited by the Examiner for teaching methods of treating sickle cell anemia by administering an antioxidant. Goodman does not disclose or suggest of the use of a NO donor (i.e. N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate) either alone or in combination with a hydralazine compound (i.e. antioxidant) for the treatment of sickle cell anemia. Additionally, hydralazine compounds are structurally very different from N-acetyl cysteine, dithiothreitol, cysteamine, dimercaprol and succimer disclosed by Goodman (see, column 8, lines 64-65 and claim 2). Hence there is no motivation for one skilled in the art to use a hydralazine compound for the treatment of treating sickle cell anemia based on the teachings in Goodman.

Goodman does not cure the deficiencies of Stamler and Adams. Goodman does not provide any motivation or suggestion to modify Stamler and Adams to arrive at the claimed invention. In view thereof, Stamler and Adams in combination with Goodman do not motivate one to arrive at the present invention.

Loscalzo is cited by the Examiner for teaching that hydralazine and hydralazine compounds are known antioxidants. Applicants respectfully submit that Loscalzo does not disclose the treatment of sickle cell anemia by the administration of a therapeutically effective amount of N- hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate in combination with hydralazine compounds. Additionally the vascular diseases disclosed by Loscalzo are very different from sickle cell anemia of the present invention. Moreover there is no suggestion or motivation by Loscalzo to treat sickle cell anemia by administering a therapeutically effective amount of N-hydroxy-L- arginine, isosorbide dinitrate or isosorbide mononitrate in combination with a hydralazine.

Loscalzo does not cure the deficiencies of Stamler, Adams and Goodman. Loscalzo does not provide any motivation or suggestion to modify Stamler, Adams and Goodman to arrive at the claimed invention. In view thereof, Stamler and Adams in combination with Goodman and Loscalzo do not motivate one to arrive at the present invention.

Examiner's response:

As mentioned in the prior office action, since Stamler teaches a method of treating sickle cell anemia comprising the administration of an NO (Nitric Oxide) donor (see claims 10, 18 and 21), and since Adams teaches that N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide mononitrate are NO (Nitric Oxide) donors (see column 3, lines 43-54), at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any NO donor) for another (N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide

mononitrate) with an expectation of success, since the prior art establishes that they function in similar manner, thus resulting in the treatment of sickle cell anemia with N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate.

The combined above references do not suggest treating sickle cell anemia with hydralazine.

However, Goodman teaches the treatment of sickle cell anemia with antioxidants (i.e. reducing agents) (see abstract, claims 1-3), and since Loscalzo teaches that hydralazine is an antioxidant, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any antioxidant) for another (hydralazine and hydralazine hydrochloride) with an expectation of success, since the prior art establishes that they function in similar manner, thus resulting in the treatment of sickle cell anemia with hydralazine.

From the above is concluded that sickle cell anemia can be treated with either: N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate or with hydralazine, as such, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat sickle cell anemia combining two compositions (a NO donor like N-hydroxy-L-arginine, isosorbide dinitrate or isosorbide mononitrate and an antioxidant like hydralazine) each of which is taught by the prior art to be useful for the same purpose (treating sickle cell anemia), in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*,

626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), thus resulting in the practice of the instant claims with a reasonable expectation of success.

The fact that the structure of hydralazine disclosed by Loscalzo is structurally very different from N-acetyl cysteine, dithiothreitol, cysteamine, dimercaprol and succimer disclosed by Goodman is irrelevant, since what is important that all these compounds, despite their structural differences are biologically equivalent, since they all act like antioxidants. Also, Loscalzo teaches N-acetyl-cysteine (see column 12, line 38), the same antioxidant disclosed by Goodman, as one of the many antioxidants, that together with hydralazine share the same biological property, as such they are expected to behave in similar way, when considering treating diseases (like sickle cell anemia) that require antioxidants.

The fact that the vascular diseases disclosed by Loscalzo are very different from sickle cell anemia of the present invention is also irrelevant, since the reference of Loscalzo is simply cited to show that hydralazine is known in the prior art as an antioxidant, regardless of what other diseases it can treat.

Finally, even though there is no single reference that teaches all the limitations, based on the above discussion it will be obvious to combine all of them in order to arrive at the present invention. The suggestions and motivations to combine them were clearly explained in the above discussion as well as in the previous office action.

The same or similar arguments are presented by Applicant regarding the rejection of claims 22-25. The only difference is the disease being treated: thalassemia instead of sickle cell anemia. So a similar response as above is provided.

The only additional issue is that Goodman does not mention thalassemia. However, it is well known in the prior art that sickle cell anemia and thalassemia share very similar charachteristics, including methods of treatment. For example, Applicant refers to Atweh (US 6,022,738) and Buhimschi et. al. (US 6,852,698) for evidentiary purposes, and not as part of the rejection itself. Atweh teaches that Sickle cell anemia and thalassemias are blood diseases caused by mutations involving the structure or expression of erythroid proteins (see c9olumn 1, lines 20-28), and allogenic bone marrow transplantation has been shown to be curative for both diseases (see lines 28-55). Buhimschi teaches that sickle cell anemia and thalassemia are hereditary anemic disorders with higher potential for oxidative damage due to chronic redox imbalance in the cells that often results in clinical manifestation of mild to serve hemolysis in patients with these disorders. Women with theses hereditary disorders have a higher risk of preterm delivery and poor neonatal outcome (see column 7, lines 28-36).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
December 31, 2009

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612